Semin Immunopathol (2009) 31:257–266
DOI 10.1007/s00281-009-0158-3

REVIEW

Disturbance of the gut-associated lymphoid tissue is associated with disease progression in chronic HIV infection

Ursula Hofer · Roberto F. Speck

Received: 9 April 2009 / Accepted: 14 May 2009 / Published online: 30 May 2009

Abstract Why and how HIV makes people sick is highly debated. Recent evidence implicates heightened immune activation due to breakdown of the gastrointestinal barrier as a determining factor of lentiviral pathogenesis. HIV-mediated loss of Th17 cells from the gut-associated lymphoid tissue (GALT) impairs mucosal integrity and innate defense mechanisms against gut microbes. Translocation of microbial products from the gut, in turn, correlates with increased immune activation in chronic HIV infection and may further damage the immune system by increasing viral and activation-induced T cell death, by reducing T cell reconstitution due to tissue scarring, and by impairing the function of other cell types, such as γδ T cells and epithelial cells. Maintaining a healthy GALT may be the key to reducing the pathogenic potential of HIV.

Keywords HIV · GALT · Microbial translocation · Immune activation · LPS · Th17 cells

Introduction

HIV infection is characterized by a progressive immunodeficiency, which is reflected in a steady decline of CD4+ T cells. Disease progression varies considerably from patient to patient. Some develop the acquired immunodeficiency syndrome (AIDS) after a few months; others remain healthy for decades. Such a disparity also exists in monkeys of distinct species infected with simian immunodeficiency virus (SIV). SIV infection of African monkeys, the natural hosts for SIV, does not result in simian AIDS, but SIV infection of most Asian monkeys rapidly progresses to AIDS [43]. Remarkably, despite 25 years of HIV and SIV research, the reasons for these differences in disease outcome are only partially understood. To design new treatment approaches, including vaccination or eradication strategies, we need to understand the basis for these disparities.

Immune dysfunction and disease onset cannot be explained solely by the direct cytopathic effect of the virus. Other factors have been implicated in T cell loss, such as the killing of infected cells by cytotoxic T cells, bystander death of uninfected cells due to HIV products, and T cell dysfunction and death due to heightened levels of immune activation [52]. A hyperactive immune state with high T cell turnover, polyclonal activation of B cells, and elevated proinflammatory cytokines is characteristic of HIV infection [52]. In fact, the activation status of CD8+ T cells is one of the best predictors of disease progression [28]. While the association of immune activation and HIV infection is well known, its causes are only partially understood.

A recent model links disturbance of the gut-associated lymphoid tissue (GALT) to immune activation and lentiviral disease progression [6]. The GALT is one of the primary organs affected by HIV and SIV, and GALT lymphocytes are the primary target cells of HIV during mucosal transmission. After rectal exposure, they are the first immune cells that encounter HIV. For infections by different routes, they form a large pool of HIV target cells, in which HIV efficiently spreads and replicates. Later on, during chronic HIV infection, loss of GALT integrity may have a major impact on AIDS pathogenesis [40]. Briefly, during the chronic phase of infection, elevated levels of

U. Hofer (✉) · R. F. Speck (✉)
Division of Infectious Diseases and Hospital Epidemiology,
University Hospital Zurich, University of Zurich,
Raemistrasse 100,
8091 Zurich, Switzerland
e-mail: ursula.hofer@usz.ch
e-mail: roberto.speck@usz.ch

microbial products are found in the systemic circulation, and these levels correlate with immune activation and disease state. Initial studies looking at interactions of lentiviruses with the GALT focused mainly on numbers of infected and dying T cells. Recently, studies have proposed cellular and molecular mechanisms that clarify the intricate role of GALT in HIV pathogenesis. Here, we will review these studies and relate their findings to lentiviral disease progression.

Profound depletion of GALT lymphocytes occurs during acute lentiviral infection

The CD4+ T cell count in the blood is a commonly used clinical marker for monitoring progression rate in HIV infection. In acute HIV infection, blood CD4+ T cell numbers may decline sharply, but as soon as an antiviral immune response is established, blood CD4+ T cells have the potential to recover. Subsequently, during chronic HIV infection, blood CD4+ T cell counts decline slowly, but this loss can be partially reversed by successful antiretroviral treatment. However, T cells in the GALT display entirely different kinetics: in SIV-infected macaques and in HIV-infected humans, CD4+ T cells of the lamina propria are rapidly and profoundly depleted in the first days after infection, and their numbers remain low throughout the course of disease [34, 51, 54]. Even after years of antiretroviral therapy, this loss is only partially reversible in most patients [17, 35]. Thus, lymphocyte depletion in the GALT is a distinct feature of lentiviral infection.

The pronounced loss of GALT lymphocytes probably occurs because the majority of newly transmitted HIV strains use CCR5 as a coreceptor for cell entry [2]. A high percentage of CD4+ T cells in the intestinal effector sites are CCR5-positive memory cells, and, thus, GALT lymphocytes are ideal viral targets. In contrast, many T cells in blood and lymph nodes are naive and hence CCR5 negative [41]. During acute SIV infection, up to 60% of all memory CD4+ T cells in the jejunum harbor HIV DNA [33], suggesting that direct viral cytopathic effects cause the massive loss of CD4+ T cells during acute infection. Furthermore, high levels of Fas-mediated apoptosis of infected and uninfected CD4+ T cells occur during peak viremia [26]. Direct viral killing and bystander death of uninfected cells wipe out most of the CD4+ memory cell population in the GALT.

When the loss of GALT lymphocytes was first discovered, it appeared plausible that this defect in mucosal immune surveillance would have dire consequences for the whole immune system and would influence disease progression. Surprisingly, however, SIV depletes lamina propria T cells in all monkey species, irrespective of whether they will develop simian AIDS or not. Natural SIV hosts, such as sooty mangabeys and African green monkeys, do not progress to AIDS despite high viral loads, but rhesus macaques infected with the same SIV strain show blood CD4+ T cell loss and disease progression, closely resembling HIV pathogenesis in humans [43]. In both the pathogenic and nonpathogenic SIV model, GALT CD4+ T cells are lost at similar rates during acute infection [15, 42]. At later times, however, the GALT can be partially restored in the nonpathogenic models. These observations indicate that acute intestinal CD4+ T cell loss is a basic feature of lentiviral infections but is not predictive of later disease outcome. Low numbers of GALT lymphocytes per se do not make animals or humans sick; additional factors are important for the pathogenic potential of HIV.

In chronic lentiviral infection, circulating microbial products are associated with immune activation

Differences in pathogenic and nonpathogenic SIV models become more apparent when GALT function, rather than simple lymphocyte numbers, is considered. The GALT prevents microbial invasions from the intestinal lumen. In chronic lentiviral infections, this function seems to be disturbed, and more microbial products are found in the systemic circulation.

Brenchely et al. [7] measured plasma levels of lipopolysaccharide (LPS), a component of gram-negative bacterial cell walls, as an indicator of microbial translocation from the gut. They found higher plasma LPS levels in chronically HIV-infected patients than in healthy subjects. Notably, a similar LPS increase was observed in the pathogenic SIV rhesus macaque model. In contrast, in the nonpathogenic SIV sooty mangabey model, LPS levels were low, irrespective of SIV status. Thus, in SIV-infected sooty mangabeys, GALT immune function appears to be sufficient to prevent increases of bacterial products in the systemic circulation despite intestinal CD4+ T cell depletion.

To further elucidate the connection between clinical outcome and microbial translocation, plasma LPS levels were examined in defined subsets of patients. For example, Hunt et al. [21] verified a finding from Brenchely et al. [7]: HIV-infected elite controllers—patients with undetectable viral loads without antiretroviral treatment—have LPS levels similar to patients with higher viral loads. At first glance, these data might indicate that no connection between plasma LPS and disease outcome exists. However, Hunt et al. showed that plasma LPS in elite controllers correlated with immune activation, which was associated with lower CD4+ T cell counts. This finding suggests that, in elite controllers, immune activation is detrimental and

leads to CD4+ T cell loss, despite suppressed plasma viral load, and that bacterial translocation may be the activating factor.

Marchetti et al. [32] investigated bacterial translocation in patients on highly active antiretroviral therapy (HAART). All patients on HAART had lower plasma levels of LPS than untreated control patients. As defined by blood CD4+ T cell reconstitution, therapy success was associated with even lower LPS levels. Patients who did not show T cell recovery despite suppressed HIV RNA had more bacterial translocation as quantified by plasma LPS than patients who responded immunologically and virologically to HAART. This means that in both groups with suppressed viral loads—either in elite controllers or in HAART-treated patients—low-level microbial translocation still occurs and seems to be associated with lower CD4+ T cell counts.

In support of the link between bacterial translocation and HIV pathogenesis, Ancuta et al. [1] found higher plasma LPS levels in patients with HIV-associated dementia than in HIV-positive patients without neurocognitive impairment. They proposed LPS-mediated monocyte activation and trafficking to the brain as the underlying mechanisms of this association between LPS and dementia. As supporting evidence, they showed upregulation of activation markers on monocytes and increases of soluble CD14, interleukin (IL)-6, and CCL2 in the plasma of HIV-infected patients.

To further investigate the effects of bacterial translocation on immune activation, Gregson et al. [16] compared plasma LPS levels in HIV-infected individuals to HIV-negative patients with active colitis, either colitis ulcerosa or morbus Crohn. All groups had similarly elevated LPS levels. However, colitis usually shows a fluctuating course: the gastrointestinal barrier, in fact, is only affected during an inflammatory phase but is relatively intact between flare-ups. In contrast, HIV-infected patients seem to experience constant bacterial translocation and immune activation.

However, factors other than bacterial translocation are thought to contribute to sustained immune activation. In particular, Gregson et al. reported that the activated phenotype of NK cells seen in their cohort of HIV-positive patients was linked to the plasma viral load and not to plasma LPS. Strikingly, the colitis patients, which had LPS levels as high as the HIV-positive patients, showed only low numbers of activated CD8+ T cells, indicating that high levels of plasma LPS alone do not cause activation of CD8+ T cells.

A study in patients undergoing interruption of antiretroviral therapy [44] supports the notion that CD8+ T cell activation not only depends on plasma LPS. In the first 6 weeks after stopping HAART, LPS levels remained unchanged, whereas percentages of activated blood CD8+ T cells increased. Only later did plasma LPS levels rise, but still no association with activated CD8+ T cells was detected, perhaps because the study examined a relatively small population. Interestingly, the delayed onset of LPS increase after treatment interruption mirrors the initial findings of Brenchely et al. [7], which also showed that, for LPS to increase, some time of sustained viral replication was required. Plasma LPS levels were similar in patients with acute HIV infection and in healthy control subjects. A possible explanation is that, initially, systemically circulating LPS can be cleared, but, over time, this function is impaired. The treatment interruption study showed a negative correlation between changes of plasma LPS levels and endotoxin core antibodies (EndoCAb) in the early phase, when plasma LPS levels are controlled. Later on, this correlation is lost. They claimed that, initially, LPS is cleared by EndoCAb, and EndoCAb levels therefore decrease. After some time, clearance is no longer effective, due either to excessive microbial translocation or to inadequate B cell function.

In conclusion, there is universal agreement that heightened levels of circulating bacterial products correlate in general with immune activation in pathogenic lentiviral infections (Table 1). However, careful interpretation is needed when deducing the mechanistic links between these events. A direct causative relation has not been established between heightened LPS levels and HIV disease progression. In an alternative explanation, microbial translocation may be an epiphenomenon of an activated and dysfunctional immune system.

Also, what is the deficit in the GALT resulting in bacterial translocation? Recent studies propose a mechanism linking depletion of a subset of GALT effector site lymphocytes, namely Th17 cells, with breakdown of the gastrointestinal barrier. Such a link is a first step in explaining the relationships between HIV infection and GALT dysfunction.

Th17 cell help is essential for the integrity of the gastrointestinal barrier

Th17 cells are important for intestinal homeostasis (reviewed in [30]). Briefly, this subset of CD4+ T cells is characterized by the production of IL-17 in response to stimulation, but they also secrete other cytokines, including tumor necrosis factor (TNF)-α, IL-1, IL-6, IL-21, and IL-22. Their strong proinflammatory properties are both beneficial and harmful. Initial animal studies identified Th17 cells as important mediators of autoimmune disease and tissue damage [24, 58], yet, with their ability to recruit neutrophils [57], they also are important for controlling infections by bacteria and fungi [18–20, 22, 31, 56]. Furthermore, Th17 cells are involved in epithelial regeneration [5]. They stimulate production of defensins and mucin [11, 53], and they induce the expression of claudins [23], which are components of epithelial tight junctions. Finally,

Table 1 Bacterial translocation in lentiviral infections

Study	Subjects	Parameters	Results
Ancuta et al. [1]	HIV in humans: progressors with or without HIV-associated dementia	LPS, sCD14, LBP, EndoCAb, IL-6, CCL2, CD16+, CD69+, or CCR5+ monocytes	Higher LPS levels in patients with dementia, association between monocyte activation, LPS, and dementia
Brenchley et al. [7]	HIV in humans: negative, acute/early, chronic, AIDS	LPS, sCD14, LBP, EndoCAb, LPS reactivity of monocytes ex vivo, plasma IFN-α, CD8+ HLA DR+ CD38+ T cells	Higher LPS levels in chronic infection, correlation with immune activation
	HIV in humans: negative, before and after HAART		LPS decrease under HAART, but no normalization
	HIV in humans: negative, controllers, progressors		Higher LPS levels in controllers compared to uninfected subjects, no significant difference to progressors
	SIV in rhesus macaques: negative, positive, positive treated with antibiotics		LPS increase after SIV infection in RMs, reduction under antibiotics
	SIV in sooty mangabeys: negative, positive		Low LPS levels in both groups of SMs
Gregson et al. [16]	HIV in humans: negative, untreated/viremic, HAART colitis: active Crohn's disease or colitis ulcerosa	LPS, CD8+ HLA DR+ CD38+ T cells, NK cell activation, LPS reactivity of NK cells ex vivo	Higher LPS levels in HIV-infected, irrespective of HAART, no difference of LPS levels between HIV-infected and colitis patients, NK and CD8+ T cell activation in HIV-infected patients, not in colitis patients
Hunt et al. [21]	HIV in humans: negative, controllers, progressors	LPS, CD8+ HLA DR+ CD38+ T cells	Higher LPS levels in controllers compared to uninfected subjects, no significant difference to progressors, correlation between activated CD8+ T cells and LPS in controllers
Marchetti et al. [32]	HIV in humans: untreated/advanced, HAART/full responders, HAART/immunological nonresponders	LPS, bacterial 16sRNA, CD4+ and CD81 Ki67+ T cells	Treatment reduced LPS levels overall, but immunological nonresponders had higher levels than full responders
Papasavvas et al. [44]	HIV in humans: HAART before and after short/long-time treatment interruption	LPS, sCD14, LBP, EndoCAb, CD8+ CD38+ T cells	No LPS increase after short-time treatment interruption, but already increase of CD8+ T cell activation; after long-time treatment interruption, LPS increase

IL-22, an important Th17 cytokine, increases the production of LPS binding protein (LBP) in the liver [55]. Considering the massive CD4+ T cell depletion in the lamina propria after HIV infection, it is reasonable to assume that Th17 cells are also depleted by HIV. And with their multiple functions in controlling epithelial integrity and microbial invasion, their loss likely affects the integrity of the gastrointestinal barrier.

While Th17 cells are permissive to HIV infection in vitro, they do not appear to be the preferential targets of HIV [8] nor of SIV [9]. Infection rates are similar in all CD4+ T cells, irrespective of Th17 or Th1 differentiation. Nevertheless, in acutely SIV-infected rhesus macaques, the intestinal Th17 responses seem to be afflicted more than the Th1 response. Checchinato et al. [9] found that the percentage of IL-17-producing cells, as related to all intestinal CD4+ T cells, was much lower, whereas the percentage of interferon-γ-producing cells was much greater than in healthy animals. Relative numbers, however, do not take into account the massive reduction of absolute CD4+ T cell numbers in the gut during acute SIV infection. Even though relative numbers of Th1 cells may be increased, the absolute numbers are still strongly reduced. It is difficult to judge the importance of relative differences between Th17 and Th1 responses in light of the overall loss of lymphocytes.

Brenchley et al. [8] further investigated the effects of HIV infection on T cell subsets at different mucosal surfaces and compared T cell responses in lung and gut. In contrast to results from bronchoalveolar lavage samples, they found a preferential depletion of IL-17-producing CD4+ T cells in the gut of HIV-infected humans. This result indicates that HIV infection especially reduces the intestinal Th17 function. In contrast to reports in humans, in SIV-infected sooty mangabeys, the relative numbers of IL-17+ CD4+ T cells in the gut are similar to those in uninfected animals. The authors linked this intact Th17 function in SIV-infected sooty mangabeys with their nonpathogenic phenotype. Again, one should be careful in interpreting relative cell numbers from the gut because of the overall depletion of CD4+ T cells.

Still, the data from both these studies suggest that the intestinal Th17 response is diminished during lentiviral infection, probably due to depletion or dysfunction of these

cells. What are now the consequences of an impaired Th17 response in the gut? Raffatellu et al. [46] addressed this question in an elegant study using a gut ligation model in rhesus macaques to study *Salmonella* translocation. Individual intestinal loops from the same animal are either mock inoculated or exposed to *Salmonella*, and immune responses then can be quantified. Intestinal *Salmonella* inoculation induced a strong mucosal Th17 response in this model. This Th17 response, however, was blunted when the rhesus macaques were chronically SIV-infected. Consequently, SIV-infected rhesus macaques had a greater degree of *Salmonella* translocation to mesenteric lymph nodes than SIV-negative monkeys. One could argue that this effect of the SIV infection on immune control of *Salmonella* translocation may not be Th17 specific but rather is due to overall GALT depletion. But Raffatellu et al. confirmed their data in mice with a targeted defect in the IL-17 receptor. Due to abrogated IL-17 signaling, these mice had less production of other IL-17-dependent cytokines upon gastrointestinal *Salmonella* inoculation, they recruited less neutrophils to the mucosa, and they were unable to control *Salmonella* translocation. The data from Raffatellu et al. corroborate the current view that HIV infection results in a loss of the intestinal Th17 response and that this affects the integrity of the gastrointestinal barrier.

In conclusion, these studies propose a model in which HIV/SIV-mediated Th17 depletion from GALT effector sites impairs the gastrointestinal barrier. This, in turn, leads to translocation of intestinal microbes or microbial products, which then contribute to immune activation (Fig. 1). However, we must be aware that no definitive experimental proof links Th17 dysfunction and elevated LPS levels. Increased intestinal *Salmonella* invasion after SIV infection is an intriguing hint but not the same as continuous translocation of harmless commensal bacteria. In Cecchinato et al. [9], for example, no correlation between LPS levels and GALT Th17 cell numbers was found in SIV-infected macaques. Nevertheless, Th17 cells probably are important in overall immunodeficiency. Recently, a defect in Th17 differentiation in patients with autosomal dominant hyper-Ig-E syndrome [36] was identified. Hyper-Ig-E syndrome is characterized by *Candida* infections, recurring pneumonia, skin abscesses, and lymphomas—a clinical picture reminiscent of AIDS. However, no data exist on the integrity of the gastrointestinal barrier and bacterial translocation in these patients.

A disturbed gastrointestinal barrier may have negative effects on the immune system

While circulating microbial products correlate well with activation markers on immune cells, the exact connection between these two phenomena is not clear. Does immune activation render the immune system so dysfunctional that it can no longer control bacterial translocation, or do the circulating bacteria and bacterial components activate the immune system and thereby contribute to the progressive immunodeficiency observed in HIV? Both possibilities likely coexist, leading to a vicious circle in which one factor triggers the other one. In any case, sustained immune activation has negative effects on T cell function and survival. For one, sustained activation provides a large pool of activated CD4+ T cells, which are optimal viral targets since HIV more efficiently infects and replicates in activated CD4+ T cells [12]. However, in most of the above studies, no positive association between plasma viral load and LPS was found [7, 44]. This is not surprising since many other factors besides overall activation status can influence viral load (e.g., HIV-specific immune responses, chemokine levels, and viral fitness).

In addition to providing a continuous reservoir of optimally activated HIV target cells, microbial products may initiate activation-induced cell death. An innovative study by Bourgeois et al. [4] in mice showed that naive CD4+ T cells are especially affected by activation-induced cell death from gut antigens. While investigating peripheral T cell dynamics after thymic ablation, they found a substantial decay in naive CD4+ T cells, while CD8+ T cell counts remained relatively stable. As the cause of CD4+ T cell activation and subsequent activation-induced death of naive cells, they identified translocation of microbial products from the gut. Indeed, the mice had higher levels of LBP, an acute-phase protein produced in the liver after exposure to LPS. Notably, in transfer experiments, they established that those CD4+ T cells reactive to gut microbes and involved in intestinal inflammation were lost specifically. Induction of intestinal inflammation by transfer of T cells reactive to gut microbes is an established tool in colitis research [29]. Naive CD4+ T cells depleted of CD25 high cells are transferred into immunodeficient mice; there, they proliferate and respond to intestinal antigens. Bourgeois et al. [4] found that CD4+ T cells from donor mice with bacterial translocation could no longer induce colitis in the recipient mice. Because of the antigen recognition and activation mechanisms in CD4+ T cells, these cells may be especially prone to effects from microbial translocation. Microbial products circulate in the extracellular compartment and are taken up by antigen-presenting cells for processing and presentation on major histocompatibility (MHC) class II molecules. Thereby, CD4+ T cells (i.e., those cells recognizing antigen in the context of MHC II) but not CD8+ T cells are activated and die.

HIV infection likely influences other immune cells in the GALT. For example, T regulatory cells (Tregs) are also affected. Tregs are abundant in the intestinal mucosa and are involved in maintaining a healthy balance between tolerance

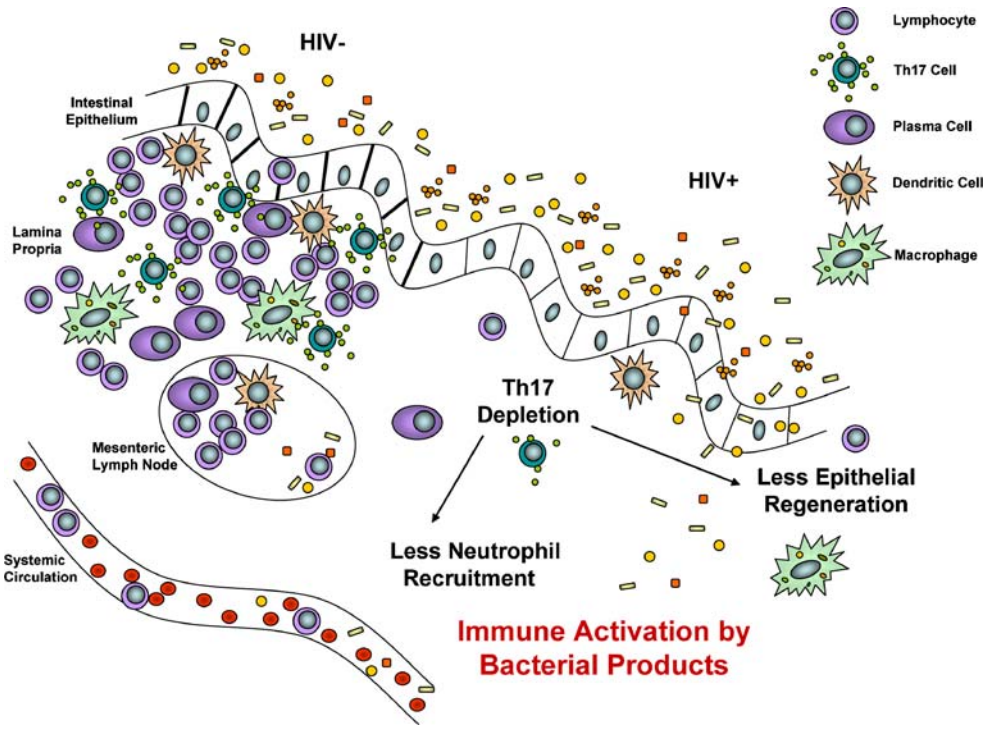

Fig. 1 HIV infection depletes lymphocytes, including Th17 cells, from the GALT effector sites. Th17 cells are essential in maintaining an intact gastrointestinal barrier against gut microbes by producing cytokines that are essential for epithelial regeneration and neutrophil recruitment. In HIV-positive individuals, circulating microbial products can be detected, and these levels correlate with immune activation

and immune control of gut microbes. Highly viremic SIV-infected macaques have more mucosal Tregs than animals with low viral loads [3]. These numerous Tregs may contribute to a less efficient SIV-specific immune response and consecutively to increased SIV loads. However, this hypothesis is controversial. Another study showed that inhibiting Treg function with a blocking antibody to CTLA-4 increased SIV replication, particularly at mucosal sites [10]. This study suggests that Tregs are protective by reducing immune activation and viral replication. Thus, increased Treg numbers in highly

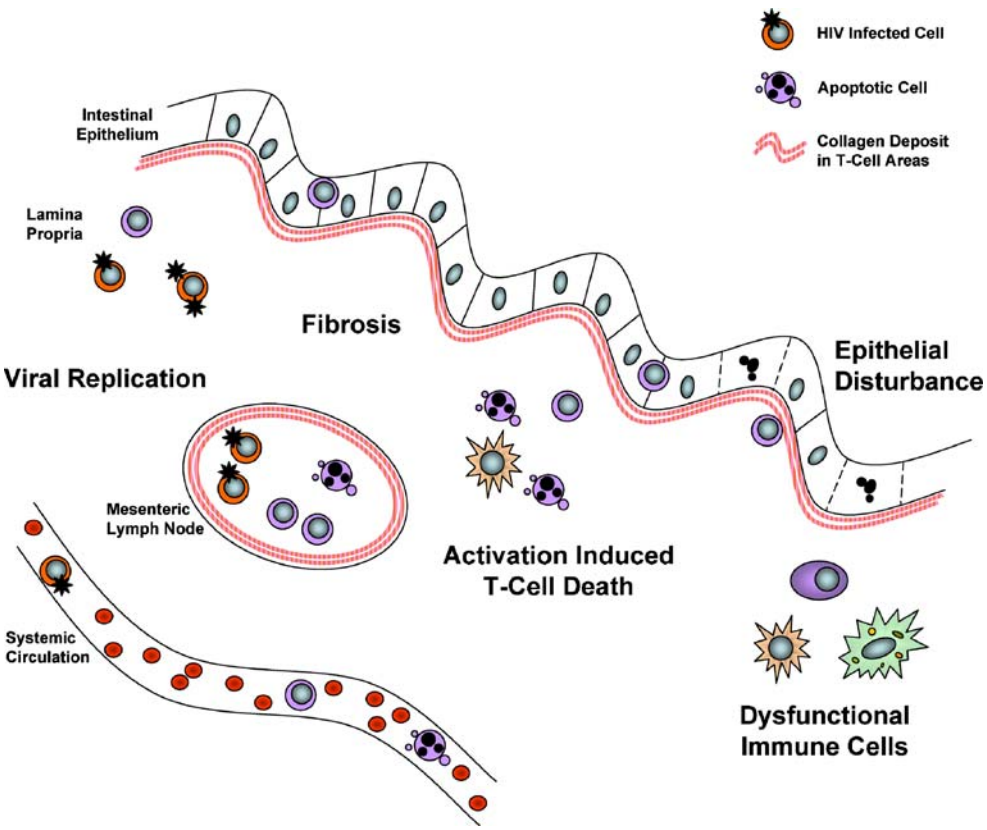

Fig. 2 Microbial translocation and ensuing immune activation can damage the immune system and contribute to HIV pathogenesis. By increasing numbers of activated cells, which are preferentially infected, microbial translocation can increase viral replication. Furthermore, activated cells are prone to activation-induced cell death, and immune reconstitution is limited due to fibrosis of the lymphatic tissue. Other immune cells, such as macrophages or γδ T cells, also are negatively affected by lentiviral infection and may be dysfunctional. Epithelial disturbance is also observed in HIV infection

viremic macaques may represent a negative regulatory feedback mechanism.

The GALT contains many cell types besides classical CD4+ T cells (e.g., plasma cells, dendritic cells, monocytes, or γδ T cells). Little is known about their fates during chronic lentiviral infection. Some studies suggest that they may be essential for limiting microbial translocation. In addition to depletion of Th17 cells, Brenchley et al. [8] also noted loss of myelomonocytic cells in the GALT of HIV-infected individuals. These myelomonocytic cells, which include granulocytes, macrophages, and dendritic cells, are essential for killing and phagocytosis of gut microbes, and for orchestrating an adaptive immune response. Another hint for the involvement of additional GALT cells in controlling microbial translocation comes from one of the nonpathogenic SIV models: sooty mangabeys, which do not show prolonged systemic LPS increases despite GALT CD4+ T cell depletion, have astoundingly high numbers of γδ T cells [7]. γδ T cells build an interface between innate and adaptive immunity and are essential for immune function at mucosal surfaces [38]. Therefore, they may have a protective effect on integrity of the intestinal barrier and may limit bacterial translocation. Compared to humans, sooty mangabeys have higher numbers of γδ T cells, and their γδ T cell response to bacterial antigens is even enhanced [37] after SIV infection. In contrast, in HIV-infected humans, γδ T cell counts are lower, and the cells are anergic to stimulation with mycobacterial antigens [45].

HIV infection also interferes with stromal and epithelial cells of the intestinal mucosa. During acute SIV infection, massive apoptosis occurs in the gut epithelium [27]. Proinflammatory genes are upregulated, and genes responsible for epithelial regeneration and digestive/metabolic functions are downregulated [47]. Notably, in chronic infection, a proinflammatory milieu marked by upregulation of IL-6 and STAT3 persists [39], and mucosal IL-2, IL-4, and TNF-α are increased, leading to increased epithelial permeability [13]. Intestinal inflammation and epithelial apoptosis not only impairs the gastrointestinal barrier, chronic inflammation also has negative effects on overall tissue architecture. GALT tissue from HIV-infected patients shows marked fibrosis, and the amount of collagen deposition is even higher than in other lymphatic organs [14]. In lymph nodes, intense fibrosis correlates with low CD4+ T cell counts and poor T cell reconstitution under HAART [49, 50], and the same very likely applies to GALT fibrosis. This observation explains the slow and poor reconstitution of GALT lymphocytes under HAART, despite suppression of the local mucosal inflammation and permeability changes mediated by successful antiretroviral treatment [13].

In summary, accumulating data indicate that HIV causes a profound and complex disturbance of the mucosal immune function. The detrimental effects of HIV are not limited to CD4+ T cells. In chronic HIV infection, disturbed GALT function and microbial translocation are accompanied by an incessant vicious circle of immune activation and inflammation with deleterious consequences on viral replication, T cell and epithelial cell death, and dysfunction of multiple additional cells (Fig. 2).

Conclusions

The GALT is one of the major organs affected by HIV infection. Viral replication and T cell loss are even more pronounced in the intestinal lamina propria than in other lymphoid tissues. Furthermore, in chronic HIV infection, a poorly controlled translocation of bacterial products (e.g., LPS) occurs and correlates with immune activation markers, which in turn are associated with disease progression. Recently, a handful of studies identified the critical role of Th17 cells in this process. During pathogenic lentiviral infections, Th17 function in the GALT is reduced and invasion of gut bacteria—directly shown so far only with *Salmonella*—is increased.

However, many questions remain. Cause and effect relations in this circle of immune dysfunction and bacterial translocation are difficult to pin down. Consequently, one cannot predict if reduction of bacterial translocation or immune activation would be a beneficial therapeutic approach. Studies with compounds blocking immune activation so far did not show positive effects [25, 48], maybe due to a general immunosuppressive effect of these drugs. Despite reduced immune activation, which may prevent further deterioration of immune functions, such drugs will also reduce immune responses directed against the virus. The optimal therapy should reduce the damaging general activation of immune cells, boost HIV-specific immune responses, and activate antimicrobial defenses at mucosal surfaces to reduce translocation of gut microbes.

Acknowledgements UH is supported by the Swiss National Science Foundation (SNSF) with a scholarship 323530-123717. RFS is supported by the SNSF (#31-118391/1).

References

1. Ancuta P, Kamat A, Kunstman KJ, Kim E-Y, Autissier P, Wurcel A, Zaman T, Stone D, Mefford M, Morgello S, Singer EJ, Wolinsky SM, Gabuzda D (2008) Microbial translocation is associated with increased monocyte activation and dementia in AIDS patients. PLoS One 3:e2516. doi:10.1371/journal.pone.0002516
2. Berger EA, Murphy PM, Farber JM (1999) Chemokine receptors as HIV-1 coreceptors: roles in viral entry, tropism, and disease.

Annu Rev Immunol 17:657–700. doi:10.1146/annurev.immunol.17.1.657
3. Boasso A, Vaccari M, Hryniewicz A, Fuchs D, Nacsa J, Cecchinato V, Andersson J, Franchini G, Shearer GM, Chougnet C (2007) Regulatory T-cell markers, indoleamine 2, 3-dioxygenase, and virus levels in spleen and gut during progressive simian immunodeficiency virus infection. J Virol 81:11593–11603. doi:10.1128/JVI.00760-07
4. Bourgeois C, Hao Z, Rajewsky K, Potocnik AJ, Stockinger B (2008) Ablation of thymic export causes accelerated decay of naive CD4 T cells in the periphery because of activation by environmental antigen. Proc Natl Acad Sci U S A 105:8691–8696. doi:10.1073/pnas.0803732105
5. Brand S, Beigel F, Olszak T, Zitzmann K, Eichhorst ST, Otte JM, Diepolder H, Marquardt A, Jagla W, Popp A, Leclair S, Herrmann K, Seiderer J, Ochsenkuhn T, Goke B, Auernhammer CJ, Dambacher J (2006) IL-22 is increased in active Crohn's disease and promotes proinflammatory gene expression and intestinal epithelial cell migration. Am J Physiol 290:G827–G838
6. Brenchley JM, Price DA, Douek DC (2006) HIV disease: fallout from a mucosal catastrophe? Nat Immunol 7:235–239. doi:10.1038/ni1316
7. Brenchley JM, Price DA, Schacker TW, Asher TE, Silvestri G, Rao S, Kazzaz Z, Bornstein E, Lambotte O, Altmann D, Blazar BR, Rodriguez B, Teixeira-Johnson L, Landay A, Martin JN, Hecht FM, Picker LJ, Lederman MM, Deeks SG, Douek DC (2006) Microbial translocation is a cause of systemic immune activation in chronic HIV infection. Nat Med 12:1365–1371. doi:10.1038/nm1511
8. Brenchley JM, Paiardini M, Knox KS, Asher AI, Cervasi B, Asher TE, Scheinberg P, Price DA, Hage CA, Kholi LM, Khoruts A, Frank I, Else J, Schacker T, Silvestri G, Douek DC (2008) Differential Th17 CD4 T-cell depletion in pathogenic and nonpathogenic lentiviral infections. Blood 112:2826–2835. doi:10.1182/blood-2008-05-159301
9. Cecchinato V, Trindade CJ, Laurence A, Heraud JM, Brenchley JM, Ferrari MG, Zaffiri L, Tryniszewska E, Tsai WP, Vaccari M, Parks RW, Venzon D, Douek DC, O'Shea JJ, Franchini G (2008) Altered balance between Th17 and Th1 cells at mucosal sites predicts AIDS progression in simian immunodeficiency virus-infected macaques. Mucosal Immunol 1:279–288. doi:10.1038/mi.2008.14
10. Cecchinato V, Tryniszewska E, Ma ZM, Vaccari M, Boasso A, Tsai W-P, Petrovas C, Fuchs D, Heraud J-M, Venzon D, Shearer GM, Koup RA, Lowy I, Miller CJ, Franchini G (2008) Immune activation driven by CTLA-4 blockade augments viral replication at mucosal sites in simian immunodeficiency virus infection. J Immunol 180:5439–5447
11. Chen Y, Thai P, Zhao YH, Ho YS, DeSouza MM, Wu R (2003) Stimulation of airway mucin gene expression by interleukin (IL)-17 through IL-6 paracrine/autocrine loop. J Biol Chem 278:17036–17043. doi:10.1074/jbc.M210429200
12. Cullen BR, Greene WC (1989) Regulatory pathways governing HIV-1 replication. Cell 58:423–426. doi:10.1016/0092-8674(89)90420-0
13. Epple HJ, Schneider T, Troeger H, Kunkel D, Allers K, Moos V, Amasheh M, Loddenkemper C, Fromm M, Zeitz M, Schulzke JD (2009) Impairment of the intestinal barrier is evident in untreated but absent in suppressively treated HIV-infected patients. Gut 58:220–227. doi:10.1136/gut.2008.150425
14. Estes J, Baker JV, Brenchley JM, Khoruts A, Barthold JL, Bantle A, Reilly CS, Beilman GJ, George ME, Douek DC, Haase AT, Schacker TW (2008) Collagen deposition limits immune reconstitution in the gut. J Infect Dis 198:456–464. doi:10.1086/590112
15. Gordon SN, Klatt NR, Bosinger SE, Brenchley JM, Milush JM, Engram JC, Dunham RM, Paiardini M, Klucking S, Danesh A, Strobert EA, Apetrei C, Pandrea IV, Kelvin D, Douek DC, Staprans SI, Sodora DL, Silvestri G (2007) Severe depletion of mucosal CD4+ T cells in AIDS-free simian immunodeficiency virus-infected sooty mangabeys. J Immunol 179:3026–3034
16. Gregson JN, Steel A, Bower M, Gazzard BG, Gotch FM, Goodier MR (2009) Elevated plasma lipopolysaccharide is not sufficient to drive natural killer cell activation in HIV-1-infected individuals. AIDS 23:29–34. doi:10.1097/QAD.0b013e3283199780
17. Guadalupe M, Reay E, Sankaran S, Prindiville T, Flamm J, McNeil A, Dandekar S (2003) Severe CD4+ T-cell depletion in gut lymphoid tissue during primary human immunodeficiency virus type 1 infection and substantial delay in restoration following highly active antiretroviral therapy. J Virol 77:11708–11717. doi:10.1128/JVI.77.21.11708-11717.2003
18. Happel KI, Dubin PJ, Zheng M, Ghilardi N, Lockhart C, Quinton LJ, Odden AR, Shellito JE, Bagby GJ, Nelson S, Kolls JK (2005) Divergent roles of IL-23 and IL-12 in host defense against *Klebsiella pneumoniae*. J Exp Med 202:761–769. doi:10.1084/jem.20050193
19. Higgins SC, Jarnicki AG, Lavelle EC, Mills KH (2006) TLR4 mediates vaccine-induced protective cellular immunity to *Bordetella pertussis*: role of IL-17-producing T cells. J Immunol 177:7980–7989
20. Huang W, Na L, Fidel PL, Schwarzenberger P (2004) Requirement of interleukin-17A for systemic anti-*Candida albicans* host defense in mice. J Infect Dis 190:624–631. doi:10.1086/422329
21. Hunt PW, Brenchley J, Sinclair E, McCune JM, Roland M, Page-Shafer K, Hsue P, Emu B, Krone M, Lampiris H, Douek D, Martin JN, Deeks SG (2008) Relationship between T cell activation and CD4+ T cell count in HIV-seropositive individuals with undetectable plasma HIV RNA levels in the absence of therapy. J Infect Dis 197:126–133. doi:10.1086/524143
22. Khader SA, Bell GK, Pearl JE, Fountain JJ, Rangel-Moreno J, Cilley GE, Shen F, Eaton SM, Gaffen SL, Swain SL, Locksley RM, Haynes L, Randall TD, Cooper AM (2007) IL-23 and IL-17 in the establishment of protective pulmonary CD4+ T cell responses after vaccination and during *Mycobacterium tuberculosis* challenge. Nat Immunol 8:369–377. doi:10.1038/ni1449
23. Kinugasa T, Sakaguchi T, Gu X, Reinecker HC (2000) Claudins regulate the intestinal barrier in response to immune mediators. Gastroenterology 118:1001–1011. doi:10.1016/S0016-5085(00)70351-9
24. Langrish CL, Chen Y, Blumenschein WM, Mattson J, Basham B, Sedgwick JD, McClanahan T, Kastelein RA, Cua DJ (2005) IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. J Exp Med 201:233–240. doi:10.1084/jem.20041257
25. Lederman MM, Smeaton L, Smith KY, Rodriguez B, Pu M, Wang H, Sevin A, Tebas P, Sieg SF, Medvik K, Margolis DM, Pollard R, Ertl HC, Valdez H (2006) Cyclosporin A provides no sustained immunologic benefit to persons with chronic HIV-1 infection starting suppressive antiretroviral therapy: results of a randomized, controlled trial of the AIDS Clinical Trials Group A5138. J Infect Dis 194:1677–1685. doi:10.1086/509261
26. Li Q, Duan L, Estes JD, Ma Z-M, Rourke T, Wang Y, Reilly C, Carlis J, Miller CJ, Haase AT (2005) Peak SIV replication in resting memory CD4+ T cells depletes gut lamina propria CD4+ T cells. Nature 434:1148–1152
27. Li Q, Estes JD, Duan L, Jessurun J, Pambuccian S, Forster C, Wietgrefe S, Zupancic M, Schacker T, Reilly C, Carlis JV, Haase AT (2008) Simian immunodeficiency virus-induced intestinal cell apoptosis is the underlying mechanism of the regenerative enteropathy of early infection. J Infect Dis 197:420–429. doi:10.1086/525046
28. Liu Z, Cumberland WG, Hultin LE, Prince HE, Detels R, Giorgi JV (1997) Elevated CD38 antigen expression on CD8+ T cells is a

stronger marker for the risk of chronic HIV disease progression to AIDS and death in the Multicenter AIDS Cohort Study than CD4 + cell count, soluble immune activation markers, or combinations of HLA-DR and CD38 expression. J Acquir Immune Defic Syndr Hum Retrovirol 16:83–92
29. Maloy KJ (2007) Induction and regulation of inflammatory bowel disease in immunodeficient mice by distinct CD4+ T-cell subsets. Methods Mol Biol 380:327–335
30. Maloy KJ, Kullberg MC (2008) IL-23 and Th17 cytokines in intestinal homeostasis. Mucosal Immunol 1:339–349. doi:10.1038/mi.2008.28
31. Mangan PR, Harrington LE, O'Quinn DB, Helms WS, Bullard DC, Elson CO, Hatton RD, Wahl SM, Schoeb TR, Weaver CT (2006) Transforming growth factor-[beta] induces development of the TH17 lineage. Nature 441:231–234. doi:10.1038/nature04754
32. Marchetti G, Bellistri GM, Borghi E, Tincati C, Ferramosca S, La Francesca M, Morace G, Gori A, Monforte AD (2008) Microbial translocation is associated with sustained failure in CD4+ T-cell reconstitution in HIV-infected patients on long-term highly active antiretroviral therapy. AIDS 22:2035–2038. doi:10.1097/QAD.0b013e3283112d29
33. Mattapallil JJ, Douek DC, Hill B, Nishimura Y, Martin M, Roederer M (2005) Massive infection and loss of memory CD4+ T cells in multiple tissues during acute SIV infection. Nature 434:1093–1097. doi:10.1038/nature03501
34. Mehandru S, Poles MA, Tenner-Racz K, Horowitz A, Hurley A, Hogan C, Boden D, Racz P, Markowitz M (2004) Primary HIV-1 infection is associated with preferential depletion of CD4+ T lymphocytes from effector sites in the gastrointestinal tract. J Exp Med 200:761–770. doi:10.1084/jem.20041196
35. Mehandru S, Poles MA, Tenner-Racz K, Jean-Pierre P, Manuelli V, Lopez P, Shet A, Low A, Mohri H, Boden D, Racz P, Markowitz M (2006) Lack of mucosal immune reconstitution during prolonged treatment of acute and early HIV-1 infection. PLoS Med 3:e484. doi:10.1371/journal.pmed.0030484
36. Milner JD, Brenchley JM, Laurence A, Freeman AF, Hill BJ, Elias KM, Kanno Y, Spalding C, Elloumi HZ, Paulson ML, Davis J, Hsu A, Asher AI, O'Shea J, Holland SM, Paul WE, Douek DC (2008) Impaired TH17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome. Nature 452:773–776. doi:10.1038/nature06764
37. Milush JM, Reeves JD, Gordon SN, Zhou D, Muthukumar A, Kosub DA, Chacko E, Giavedoni LD, Ibegbu CC, Cole KS, Miamidian JL, Paiardini M, Barry AP, Staprans SI, Silvestri G, Sodora DL (2007) Virally induced CD4+ T cell depletion is not sufficient to induce AIDS in a natural host. J Immunol 179:3047–3056
38. Modlin RL, Sieling PA (2005) Immunology: now presenting: γδ T cells. Science 309:252–253. doi:10.1126/science.1115264
39. Mohan M, Aye PP, Borda JT, Alvarez X, Lackner AA (2007) Gastrointestinal disease in simian immunodeficiency virus-infected rhesus macaques is characterized by proinflammatory dysregulation of the interleukin-6-Janus kinase/signal transducer and activator of transcription 3 pathway. Am J Pathol 171:1952–1965. doi:10.2353/ajpath.2007.070017
40. Paiardini M, Frank I, Pandrea I, Apetrei C, Silvestri G (2008) Mucosal immune dysfunction in AIDS pathogenesis. AIDS Rev 10:36–46
41. Pandrea I, Apetrei C, Gordon S, Barbercheck J, Dufour J, Bohm R, Sumpter B, Roques P, Marx PA, Hirsch VM, Kaur A, Lackner AA, Veazey RS, Silvestri G (2007) Paucity of CD4+ CCR5+ T cells is a typical feature of natural SIV hosts. Blood 109:1069–1076. doi:10.1182/blood-2006-05-024364
42. Pandrea IV, Gautam R, Ribeiro RM, Brenchley JM, Butler IF, Pattison M, Rasmussen T, Marx PA, Silvestri G, Lackner AA, Perelson AS, Douek DC, Veazey RS, Apetrei C (2007) Acute loss of intestinal CD4+ T cells is not predictive of simian immunodeficiency virus virulence. J Immunol 179:3035–3046
43. Pandrea I, Sodora DL, Silvestri G, Apetrei C (2008) Into the wild: simian immunodeficiency virus (SIV) infection in natural hosts. Trends Immunol 29:419–428. doi:10.1016/j.it.2008.05.004
44. Papasavvas E, Pistilli M, Reynolds G, Bucki R, Azzoni L, Chehimi J, Janmey PA, DiNubile MJ, Ondercin J, Kostman JR, Mounzer KC, Montaner LJ (2009) Delayed loss of control of plasma lipopolysaccharide levels after therapy interruption in chronically HIV-1-infected patients. AIDS 23:369–375. doi:10.1097/QAD.0b013e32831e9c76
45. Poccia F, Boullier S, Lecoeur H, Cochet M, Poquet Y, Colizzi V, Fournie JJ, Gougeon ML (1996) Peripheral V gamma 9/V delta 2 T cell deletion and anergy to nonpeptidic mycobacterial antigens in asymptomatic HIV-1-infected persons. J Immunol 157:449–461
46. Raffatellu M, Santos RL, Verhoeven DE, George MD, Wilson RP, Winter SE, Godinez I, Sankaran S, Paixao TA, Gordon MA, Kolls JK, Dandekar S, Baumler AJ (2008) Simian immunodeficiency virus-induced mucosal interleukin-17 deficiency promotes *Salmonella* dissemination from the gut. Nat Med 14:421–428. doi:10.1038/nm1743
47. Sankaran S, George MD, Reay E, Guadalupe M, Flamm J, Prindiville T, Dandekar S (2008) Rapid onset of intestinal epithelial barrier dysfunction in primary human immunodeficiency virus infection is driven by an imbalance between immune response and mucosal repair and regeneration. J Virol 82:538–545. doi:10.1128/JVI.01449-07
48. Sankatsing SU, Jurriaans S, van Swieten P, van Leth F, Cornelissen M, Miedema F, Lange JM, Schuitemaker H, Prins JM (2004) Highly active antiretroviral therapy with or without mycophenolate mofetil in treatment-naive HIV-1 patients. AIDS 18:1925–1931. doi:10.1097/00002030-200409240-00008
49. Schacker TW, Nguyen PL, Beilman GJ, Wolinsky S, Larson M, Reilly C, Haase AT (2002) Collagen deposition in HIV-1 infected lymphatic tissues and T cell homeostasis. J Clin Invest 110:1133–1139
50. Schacker TW, Brenchley JM, Beilman GJ, Reilly C, Pambuccian SE, Taylor J, Skarda D, Larson M, Douek DC, Haase AT (2006) Lymphatic tissue fibrosis is associated with reduced numbers of naive CD4+ T cells in human immunodeficiency virus type 1 infection. Clin Vaccine Immunol 13:556–560. doi:10.1128/CVI.13.5.556-560.2006
51. Schneider T, Jahn HU, Schmidt W, Riecken EO, Zeitz M, Ullrich R (1995) Loss of CD4 T lymphocytes in patients infected with human immunodeficiency virus type 1 is more pronounced in the duodenal mucosa than in the peripheral blood. Berlin Diarrhea/Wasting Syndrome Study Group. Gut 37:524–529. doi:10.1136/gut.37.4.524
52. Sodora DL, Silvestri G (2008) Immune activation and AIDS pathogenesis. AIDS 22:439–446. doi:10.1097/QAD.0b013e3282f2dbe7
53. Sugimoto K, Ogawa A, Mizoguchi E, Shimomura Y, Andoh A, Bhan AK, Blumberg RS, Xavier RJ, Mizoguchi A (2008) IL-22 ameliorates intestinal inflammation in a mouse model of ulcerative colitis. J Clin Invest 118:534–544
54. Veazey RS, DeMaria M, Chalifoux LV, Shvetz DE, Pauley DR, Knight HL, Rosenzweig M, Johnson RP, Desrosiers RC, Lackner AA (1998) Gastrointestinal tract as a major site of CD4+ T cell depletion and viral replication in SIV infection. Science 280:427–431. doi:10.1126/science.280.5362.427
55. Wolk K, Witte E, Hoffmann U, Doecke WD, Endesfelder S, Asadullah K, Sterry W, Volk HD, Wittig BM, Sabat R (2007) IL-22 induces lipopolysaccharide-binding protein in hepatocytes: a potential systemic role of IL-22 in Crohn's disease. J Immunol 178:5973–5981

56. Wu Q, Martin RJ, Rino JG, Breed R, Torres RM, Chu HW (2007) IL-23-dependent IL-17 production is essential in neutrophil recruitment and activity in mouse lung defense against respiratory *Mycoplasma pneumoniae* infection. Microbes Infect/Institut Pasteur 9:78–86
57. Ye P, Rodriguez FH, Kanaly S, Stocking KL, Schurr J, Schwarzenberger P, Oliver P, Huang W, Zhang P, Zhang J, Shellito JE, Bagby GJ, Nelson S, Charrier K, Peschon JJ, Kolls JK (2001) Requirement of interleukin 17 receptor signaling for lung CXC chemokine and granulocyte colony-stimulating factor expression, neutrophil recruitment, and host defense. J Exp Med 194:519–528. doi:10.1084/jem.194.4.519
58. Yen D, Cheung J, Scheerens H, Poulet F, McClanahan T, McKenzie B, Kleinschek MA, Owyang A, Mattson J, Blumenschein W, Murphy E, Sathe M, Cua DJ, Kastelein RA, Rennick D (2006) IL-23 is essential for T cell-mediated colitis and promotes inflammation via IL-17 and IL-6. J Clin Invest 116:1310–1316. doi:10.1172/JCI21404